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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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KENNETH P. ZWICKER
ABBOTT BIORESEARCH CENTER
100 RESEARCH DRIVE
WORCESTER, MA 01605

EXAMINER	
ANDRES, JANET L	

ART UNIT	PAPER NUMBER
1646	

DATE MAILED: 08/02/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/894,550	COLLINSON ET AL.	
	Examiner	Art Unit	
	Janet L. Andres	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 June 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-95* is/are pending in the application.

4a) Of the above claim(s) *5-8, 11, and 32-88* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,9,10,12-31 and 89-95* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 7 June 2004 has been entered. Claims 1-95 are pending in this office action. Claims 1-4, 9, 10, 12-31, and 89-95 are under examination. Claims 5-8, 11, and 32-88 are withdrawn from consideration as being drawn to a non-elected invention. The text of those sections of Title 35, U.S. Code, not included in this action can be found in a prior office action.

Claim Rejections - 35 USC § 103

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later

invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

3. Claims 1-4, 9, 12-14, 16, 28, 29, 31, and 89 are rejected under 35 U.S.C. 103(a) as being unpatentable over Luger et al., Immunobiology, 1986, vol. 172, pp. 346-356, in view of Green, J. Immunological Methods 1999, Vol. 231, pp. 11-23.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Luger et al. teaches a monoclonal antibody that reacts with and inhibits the activity of both interleukin 1α and interleukin 1β. See p. 354. Luger et al. concludes that this antibody binds to a shared epitope of interleukin 1. Thus, Luger et al. teach an antibody that reacts with and inhibits IL-1α and β, as specified in claims 1-3 and 31. The antibody was generated in mice using a common structural feature of the two molecules, as specified in claims 4 and 12-14. Luger et al. further teaches that IL-1 is involved in inflammatory disease (pp. 346 and 354) and states that this involvement is the rationale for developing the antibody and would be useful to investigate the role of IL-1 during inflammatory disease (abstract, p. 346).

Lugar et al. fails to teach the hybrid molecule specified in instant claim 9. However, it would be obvious to the artisan of ordinary skill to make such a molecule, because Lugar et al. teaches that this is the region that generates the dually specific antibody. Thus the artisan of

ordinary skill would expect results at least as good from using the particular antigen of choice, rather than molecule with other antigenic regions.

Luger et al. additionally fails to teach the use of transgenic mice for the production of human antibodies or other means of producing antibodies that are not fully mouse. Green teaches XenoMouse™ strains, which are transgenic mice that generate human antibodies (see abstract). Green teaches that there are disadvantages to murine antibodies (p. 12, column 1) and that chimeric antibodies have been used to overcome these disadvantages (p. 12, column 2). Green further teaches that the disadvantages of murine antibodes are overcome by using XenoMouse™ strains to generate antibodies (p. 20, column 1). Green fails to teach the use of these mice to generate antibodies against IL-1 or the use of chimeric anti-IL-1 antibodies. However, it would have been obvious to one of ordinary skill in the art to combine the teachings of Green with those of Luger et al. to produce humanized IL-1 antibodies or to produce chimeric antibodies. One of ordinary skill would be motivated to do so because Luger et al. teaches that IL-1 is involved in inflammation and can be inhibited by a monoclonal antibody, and Green teaches methods of making a more useful form of such an antibody. Thus one of ordinary skill would expect to be able to produce a superior monoclonal antibody for use in inhibiting the effects of IL-1 in inflammation using the approaches set forth by Green.

4. Claims 1-4, 9, 12-14, 17, 28, 31, and 89 are rejected under 35 U.S.C. 103(a) as unpatentable over Luger et al. in view of Nguyen et al., Microbiol Immunol. 1997, vol. 41(12), pp. 901-907.

Luger et al. teaches as set forth in paragraphs 5 and 7 above but fails to teach SCID mice reconstituted with human cells or other means of producing antibodies that are not fully mouse.

Nguyen et al. teaches that such mice are useful for the production of human monoclonal antibodies and teaches the advantages of such antibodies (p. 901, column 1, p. 905, column 2, p. 906, column 1). Nguyen fails to teach antibodies against IL-1. However, it would be obvious to one of ordinary skill in the art to combine the teachings of Nguyen et al with those of Luger et al. to produce human IL-1 antibodies. One of ordinary skill would have been motivated to do so because Luger et al. teaches that IL-1 is involved in inflammation and can be inhibited by a monoclonal antibody, and Nguyen et al. teaches a method of making a more useful form of such an antibody. Thus one of ordinary skill would expect to be able to produce a superior monoclonal antibody for use in inhibiting the effects of IL-1 in inflammation.

5. Claims 1-4, 9, 12-14, 18, 28, and 31 are rejected under 35 U.S.C. (a) as unpatentable over Luger et al. in view of Reisner et al., Tibtech, 1998, vol. 16, pp. 242-246.

Luger et al. teaches as set forth in paragraph 3 above but fails to teach irradiated mice protected by bone marrow cells of SCID mice and engrafted with human lymphocytes or other means of producing antibodies that are not fully mouse. Such mice are taught by Reisner et al. Reisner et al. further teaches that these mice can be used for generating human monoclonal antibodies (p. 242, column 2, p. 243, p. 244) and that such antibodies are useful therapeutically (p. 243). Reisner et al. fails to teach antibodies against IL-1. However, it would be obvious to one of ordinary skill in the art to combine the teachings of Reisner et al. with those of Luger et al. to produce human IL-1 antibodies. One of ordinary skill would have been motivated to do so because Luger et al. teaches that IL-1 is involved in inflammation and can be inhibited by a monoclonal antibody and Reisner et al. teaches a method of making a more useful form of such

an antibody. Thus one of ordinary skill would expect to be able to produce a superior monoclonal antibody for use in inhibiting the effects of IL-1 in inflammation.

6. Claims 1-4, 9, 12-14, 19, 20, 24, and 31 are rejected under 35 U.S.C. 103(a) as unpatentable over Luger et al. in view of Barbas et al., Proc. Nat. Acad. Sci. 1991, vol. 88, pp. 7978-7982.

Luger et al. teaches as set forth in paragraph 3 above but fails to teach combinatorial antibody libraries or the expression of such libraries on phage surfaces, as claimed in claim 20 or other means of producing antibodies that are not fully mouse. Barbas et al. teaches display of combinatorial antibody libraries on the surface of phage M13 and teaches the use of the use of such libraries to generate antitetanus toxoid antibodies on p. 7980. The library used was an Fab library (see abstract and p. 7979, column 1), as specified in claim 24. Barbas et al. further teaches that such methods are useful for selection of clones of defined specificity and high affinity (p. 7981). Barbas et al. fails to teach antibodies against IL-1. However, it would have been obvious to one of ordinary skill in the art to combine the teachings of Barbas et al. with those of Luger et al. to produce antibodies against IL-1 using phage display. One of ordinary skill would have been motivated to do so because Luger et al. teaches that anti-IL-1 antibodies are useful for therapeutic and research purposes and Barbas et al. teaches a superior method of making such antibodies.

7. Claims 1-4, 9, 12-14, 19, 21, and 31 are rejected under 35 U.S.C. 103(a) as unpatentable over Luger et al. in view of WO 99/36569, Wittrup et al., 1999.

Luger et al. teaches as set forth in paragraph 3 above but fails to teach combinatorial antibody libraries or their display on yeast cells, as claimed in claim 21, or other means of

producing antibodies that are not fully mouse. WO 99/36569 teaches such yeast selection systems and teaches on pp. 20-21 that these systems are particularly suited for antibodies. WO 99/36569 fails to teach antibodies against IL-1. However, it would be obvious to one of ordinary skill in the art to combine the teachings of WO 99/36569 with those of Luger et al. to produce antibodies against IL-1 using display on yeast cells. One of ordinary skill would have been motivated to do so because Luger et al. teaches that anti-IL-1 antibodies are useful for therapeutic and research purposes and WO 99/36569 teaches a superior method of making such antibodies.

8. Claims 1-4, 9, 12-14, 19, 21, 22, and 31 are rejected under 35 U.S.C. 103(a) as unpatentable over Luger et al. in view of WO 98/49286, Iverson et al., 1998.

Luger et al. teaches as set forth in paragraph 3 above but fails to teach recombinant antibody libraries or their display on yeast cells, as claimed in claim 21, or bacterial cells, as claimed in claim 22, or other means of producing antibodies that are not fully mouse. WO 98/49286 teaches expression libraries for antibodies and their expression on yeast cells on p. 5, line 7 and on bacterial cells on p. 5, lines 20-31, for example. W) 98/49286 teaches that this system is advantageous because it allows for rapid and efficient selection, purification, and screening (p. 13, lines 29-31 and p. 14, lines 1-5). WO 98/49286 fails to teach antibodies against IL-1. However, it would be obvious to one of ordinary skill in the art to combine the teachings of WO 98/49286 with those of Luger et al. to produce antibodies against IL-1 using display on yeast cells. One of ordinary skill would have been motivated to do so because Luger et al. teaches that anti-IL-1 antibodies are useful for therapeutic and research purposes and WO 98/49286 teaches a superior method of making such antibodies.

9. Claims 1-4, 9, 12-14, 19, 23, and 31 are rejected under 35 U.S.C. 103(a) as unpatentable over Luger et al. in view of WO 98/31700.

Luger et al. teaches as set forth in paragraph 3 above but fails to teach RNA-protein fusions as claimed in claim 23 or other means of producing antibodies that are not fully mouse. WO 98/31700 teaches such fusions and teaches that they can be used to improve human or humanized antibodies on p. 64, lines 18-29, and p. 65, lines 1-7. WO 98/31700 fails to teach antibodies against IL-1. However, it would be obvious to one of ordinary skill in the art to combine the teachings of WO 98/31700 with those of Luger et al. to produce antibodies against IL-1 using display on yeast cells. One of ordinary skill would have been motivated to do so because Luger et al. teaches that anti-IL-1 antibodies are useful for therapeutic and research purposes and 98/31700 teaches a superior method of making such antibodies.

10. Claim 1-4, 9, 12-14, 25, and 31 are rejected under 35 U.S.C. 103(a) as unpatentable over Luger et al. in view of U.S. patent 5580717, Dower et al., 1996.

Luger et al. teaches as set forth in paragraph 3 above but fails to teach *in vitro* screening as claimed in claim 23 or other means of producing antibodies that are not fully mouse. The '717 patent teaches such a method; see column 4, lines 2-41. The '717 patent further teaches that this is a useful method for screening large libraries and that this advantage is particularly significant for antibodies in column 1, lines 28-50. The '717 patent fails to teach antibodies against IL-1. However, it would be obvious to one of ordinary skill in the art to combine the teachings of the '717 patent with those of Luger et al. to produce antibodies against IL-1 using a recombinant antibody library prepared from immunized animals. One of ordinary skill would have been motivated to do so because Luger et al. teaches that anti-IL-1 antibodies are useful for

therapeutic and research purposes and '717 patent teaches a method that allows the screening of large numbers of such antibodies.

11. Claim 1-4, 9, 12-14, 26, and 31 are rejected under 35 U.S.C. 103(a) as unpatentable over Luger et al. in view of WO 9729131, Salfeld et al., 1997.

Luger et al. teaches as set forth in paragraphs 3 above but fails to teach *in vitro* maturation or other means of producing antibodies that are not fully mouse. WO 97/29131 teaches the generation of high-affinity TNF-α antibodies using this approach: see pages 18-21. WO 97/29131 further teaches that these antibodies are neutralizing, bind with high affinity, and have slow dissociation kinetics. WO 97/29131 fails to teach antibodies against IL-1. However, it would be obvious to one of ordinary skill in the art to combine the teachings of WO 97/29131 with those of Luger et al. to produce antibodies against IL-1 using *in vitro* maturation. One of ordinary skill would have been motivated to do so because Luger et al. teaches that anti-IL-1 antibodies are useful for therapeutic and research purposes and WO 97/29131 teaches a method that produces antibodies with the desirable characteristics of high affinity, slow dissociation, and neutralization.

12. Claim 1-4, 9, 12-14, 27, 31, and 95 are rejected under 35 U.S.C. 103(a) as unpatentable over Luger et al. in view of Babcock et al., Proc. Nat. Acad. Sci., 1996, vol. 93, pp. 7843-7848.

Luger et al. teaches as set forth in paragraph 3 above but fails to teach selection of single cells and recovery of variable regions or other means of producing antibodies that are not fully mouse. Babcock et al. teaches this method: see, for example, the discussion section on pp. 7847-7848. Babcock et al. further teaches that this method can be used to produce antibodies with specific characteristics (p. 7847, column 1) and would be particularly useful for the

generation of humanized antibodies for medical applications (p. 7848, column 1). Babcock et al. fails to teach antibodies against IL-1. However, it would be obvious to one of ordinary skill in the art to combine the teachings of Babcock et al. with those of Luger et al. to produce antibodies against IL-1 using the method of Babcock et al. One of ordinary skill would have been motivated to do so because Luger et al. teaches that anti-IL-1 antibodies are useful for therapeutic and research purposes and Babcock et al. teaches a method that produces antibodies with particular characteristics and is particularly useful for producing humanized antibodies for therapeutic use.

13. Claims 1-4, 9, 12-14, 29, 30, 31, and 90-94 are rejected under 35 U.S.C. 103(a) as being unpatentable over Luger et al. in view of Knappik et al., JMB, Feb. 2000, vol. 296, pp. 57-86.

Luger et al. teaches as set forth in paragraph 3 above but fails to teach chimeras or CDR-grafted antibodies or other means of producing antibodies that are not fully mouse. Knappik et al. teaches chimeric antibodies as a useful alternative to purely rodent antibodies on p. 58, column 1. Knappik et al. further teaches generation of CDR-grafted antibodies as a means of generating high affinity binders; see the abstract, for example. Knappik et al. fails to teach antibodies against IL-1. However, it would be obvious to one of ordinary skill in the art to combine the teachings of Knappik et al. with those of Luger et al. to produce chimeric or CDR-grafted antibodies against IL-1. One of ordinary skill would have been motivated to do so because Luger et al. teaches that anti-IL-1 antibodies are useful for therapeutic and research purposes and Knappik et al. teaches methods that produce antibodies that avoid the difficulties associated with therapeutic use of rodent antibodies.

Claim Rejections - 35 USC § 112

14. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

15. Claims 1-4, 12-31, and 89-95 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for not fully mouse versions of the antibody characterized by Luger et al. and Kock et al. (J. Exp. Med., 1896, vol. 163, no. 2, pp. 463-468), as well as those generated by SEQ ID NO 3, does not reasonably provide enablement for all dual-specificity antibodies and means of making them. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The factors to be considered have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art and the breadth of the claims. *Ex Parte Forman,* (230 USPQ 546 (Bd Pat. App. & Int. 1986)); *In re Wands,* 858 F.2d 731, 8 USPQ 2d 1400 (Fed. Cir. 1988).

The prior art describes one dual-specificity antibody (Lugar and Kock appear to use the same antibody), and Applicant discloses on p. 49-50 that dual specificity antibodies were raised against the peptide of SEQ ID NO: 3. However, the other three peptides tested were unable to produce dual specificity antibodies. Thus, Applicant has described one dual specificity antibody and the prior art teaches another. However, claims 1-3 encompass all dual specificity antibodies

and claims 12-31 encompass all antibodies generated by a "common structural feature". Applicant has not described the characteristics of peptides that generate dual specificity antibodies so that one of skill in the art could predictably identify other such peptides as broadly claimed. No peptides other than the one containing the overlapping region of IL-1α and IL-1β are taught to be able to generate a dual specificity antibody. The disclosure of this peptide does not serve to teach what other, structurally unrelated peptides could be used, nor does it teach the necessary characteristics of other peptides containing the overlapping region. There is no direction as to what other sequences could be added to the enabled peptide, or what other alterations could be made that would still result in a peptide that generated a dual specificity antibody, and no other required structural features are set forth to provide such guidance. Thus, the essential characteristics of peptides able to generate dual specificity antibodies are not described. Further, it is not routine in the art to screen large numbers of peptides that might potentially generate such antibodies where the expectation of obtaining similar specificity is unpredictable. The prior art does not provide compensatory teachings; while Kock et al. and Luger et al. presume there is a common structural feature that served as an epitope, they do no not disclose its nature. Thus one of skill in the art would require additional guidance, such as information as to what structural features are required to generate such antibodies, or what other peptides could be used, in order to practice the invention commensurate with the scope of the claims without undue experimentation.

Allowable Subject Matter

16. Claim 10 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

CLAIMS 1-4, 9, 12-31, AND 89-95 ARE REJECTED. CLAIM 10 IS OBJECTED TO.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janet L. Andres whose telephone number is 571-272-0867. The examiner can normally be reached on Monday-Thursday and every other Friday, 8:00-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback can be reached on 571-272-0961. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Janet L. Andres, Ph.D.
29 July 2004

JANET ANDRES
PRIMARY EXAMINER